Eryhtropoietin production potentiator

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 NEWS 19  MAR 01  INSPEC reloaded and enhanced
 NEWS 20  MAR 03  Updates in PATDPA; addition of IPC 8 data without attributes
 NEWS 21  MAR 08  X.25 communication option no longer available after June 2006
 NEWS 22  MAR 22  EMBASE is now updated on a daily basis

 NEWS EXPRESS  FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
               V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
               http://download.cas.org/express/v8.0-Discover/

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FILE 'HOME' ENTERED AT 17:33:15 ON 27 MAR 2006

=> file medline biosis
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'MEDLINE' ENTERED AT 17:33:27 ON 27 MAR 2006

FILE 'BIOSIS' ENTERED AT 17:33:27 ON 27 MAR 2006
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=> s erythropoietin
L1       36917 ERYTHROPOIETIN

=> s GATA
L2        6885 GATA

=> s L1 and L2
L3         328 L1 AND L2

=> s L3 and py<2003
   1 FILES SEARCHED...
L4         245 L3 AND PY<2003

=> s L3 and py<2002
   1 FILES SEARCHED...
L5         216 L3 AND PY<2002

=> s L5 and K-7174
L6           0 L5 AND K-7174

=> s K-7174
L7           9 K-7174

=> s L7 and L2
L8           8 L7 AND L2
```

Eryhtropoietin production potentiator

=> s L7 and L1
L9 5 L7 AND L1

=> d L9 1-5 ti abs bib

L9 ANSWER 1 OF 5 MEDLINE on STN
TI Oral administration of K-11706 inhibits GATA binding activity, enhances hypoxia-inducible factor 1 binding activity, and restores indicators in an in vivo mouse model of anemia of chronic disease.
AB **Erythropoietin** (Epo) gene expression is under the control of hypoxia-inducible factor 1 (HIF-1), and is negatively regulated by GATA. Interleukin 1beta (IL-1beta) and tumor necrosis factor alpha (TNF-alpha), which increase the binding activity of GATA and inhibit Epo promoter activity, are increased in patients with anemia of chronic disease (ACD). We previously demonstrated the ability of **K-7174** (a GATA-specific inhibitor), when injected intraperitoneally, to improve Epo production that had been inhibited by IL-1beta or TNF-alpha treatment. In the present study, we examined the ability of both K-11706, which inhibits GATA and enhances HIF-1 binding activity, and K-13144, which has no effect on GATA or HIF-1 binding activity, to improve Epo production following inhibition by IL-1beta or TNF-alpha in Hep3B cells in vitro and in an in vivo mouse assay. Oral administration of K-11706 reversed the decreases in hemoglobin and serum Epo concentrations, reticulocyte counts, and numbers of erythroid colony-forming units (CFU-Es) induced by IL-1beta or TNF-alpha. These results raise the possibility of using orally administered K-11706 for treating patients with ACD.
AN 2004605486 MEDLINE
DN PubMed ID: 15328158
TI Oral administration of K-11706 inhibits GATA binding activity, enhances hypoxia-inducible factor 1 binding activity, and restores indicators in an in vivo mouse model of anemia of chronic disease.
AU Nakano Yoko; Imagawa Shigehiko; Matsumoto Ken; Stockmann Christian; Obara Naoshi; Suzuki Norio; Doi Takeshi; Kodama Tatsuhiko; Takahashi Satoru; Nagasawa Toshiro; Yamamoto Masayuki
CS Division of Hematology, Institute of Clinical Medicine, Center for Tsukuba Advanced Research Alliance, University of Tsukuba, Tsukuba, Ibaraki 305-8575, Japan.
SO Blood, (2004 Dec 15) Vol. 104, No. 13, pp. 4300-7. Electronic Publication: 2004-08-24.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200503
ED Entered STN: 20041207
Last Updated on STN: 20050325
Entered Medline: 20050324

L9 ANSWER 2 OF 5 MEDLINE on STN
TI A GATA-specific inhibitor (**K-7174**) rescues anemia induced by IL-1beta, TNF-alpha, or L-NMMA.
AB Interleukin-1beta (IL-1beta), tumor necrosis factor-alpha (TNF-alpha), or N(G)-monomethyl-L-arginine (L-NMMA) are increased in patients with chronic disease-related anemia. They increase the binding activity of GATA and inhibit **erythropoietin** (Epo) promoter activity. In this study, we examined the ability of **K-7174** (a GATA-specific inhibitor) to improve Epo production when inhibited by treatment with IL-1beta, TNF-alpha, or L-NMMA. Epo protein production and promoter activity were induced in Hep3B cells with 1% O2. However, 15 U/ml IL-1beta, 220 U/ml TNF-alpha, or 10(-3) M L-NMMA inhibited Epo protein production and promoter activity, respectively. Addition of 10 microM **K-7174** rescued these inhibitions of Epo protein

production and promoter activity induced by IL-1beta, TNF-alpha, or L-NMMA, respectively. Electrophoretic mobility shift assays revealed that addition of **K-7174** decreased GATA binding activity, which was increased with the addition of IL-1beta, TNF-alpha, or L-NMMA. Furthermore, intraperitoneal injection of mice with IL-1beta or TNF-alpha decreased the hemoglobin concentrations and reticulocyte counts. However, the addition of **K-7174** reversed these effects. These results raise the possibility of using **K-7174** as therapy to treat anemia.

AN 2003419245 MEDLINE
DN PubMed ID: 12958195
TI A GATA-specific inhibitor (**K-7174**) rescues anemia induced by IL-1beta, TNF-alpha, or L-NMMA.
AU Imagawa Shigehiko; Nakano Yoko; Obara Naoshi; Suzuki Norio; Doi Takeshi; Kodama Tatsuhiko; Nagasawa Toshiro; Yamamoto Masayuki
CS Division of Hematology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Ibaraki 305-8575, Japan.. simigawa@md.tsukuba.ac.jp
SO The FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2003 Sep) Vol. 17, No. 12, pp. 1742-4. Electronic Publication: 2003-07-18.
Journal code: 8804484. E-ISSN: 1530-6860.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200310
ED Entered STN: 20030909
Last Updated on STN: 20031009
Entered Medline: 20031008

L9 ANSWER 3 OF 5 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI Oral administration of K-11706 inhibits GATA binding activity, enhances hypoxia-inducible factor 1 binding activity, and restores indicators in an in vivo mouse model of anemia of chronic disease.
AB **Erythropoietin** (Epo) gene expression is under the control of hypoxia-inducible factor 1 (HIF-1), and is negatively regulated by GATA. Interleukin 1beta (IL-1beta) and tumor necrosis factor alpha (TNF-alpha), which increase the binding activity of GATA and inhibit Epo promoter activity, are increased in patients with anemia of chronic disease (ACD). We previously demonstrated the ability of **K-7174** (a GATA-specific inhibitor), when injected intraperitoneally, to improve Epo production that had been inhibited by IL-1beta or TNF-alpha treatment. In the present study, we examined the ability of both K-11706, which inhibits GATA and enhances HIF-1 binding activity, and K-13144, which has no effect on GATA or HIF-1 binding activity, to improve Epo production following inhibition by IL-1beta or TNF-alpha in Hep3B cells in vitro and in an in vivo mouse assay. Oral administration of K-11706 reversed the decreases in hemoglobin and serum Epo concentrations, reticulocyte counts, and numbers of erythroid colony-forming units (CFU-Es) induced by IL-1beta or TNF-alpha. These results raise the possibility of using orally administered K-11706 for treating patients with ACD. Copyright 2004 by The American Society of Hematology.
AN 2005:74408 BIOSIS
DN PREV200500069193
TI Oral administration of K-11706 inhibits GATA binding activity, enhances hypoxia-inducible factor 1 binding activity, and restores indicators in an in vivo mouse model of anemia of chronic disease.
AU Nakano, Yoko; Imagawa, Shigehiko [Reprint Author]; Matsumoto, Ken; Stockmann, Christian; Obara, Naoshi; Suzuki, Norio; Doi, Takeshi; Kodama, Tatsuhiko; Takahashi, Satoru; Nagasawa, Toshiro; Yamamoto, Masayuki
CS Inst Clin MedDiv HematolCtr Tsukuba Adv Res Alliance, Univ Tsukuba, Tsukuba, Ibaraki, 3058575, Japan
simagawa@md.tsukuba.ac.jp

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SO Blood, (December 15 2004) Vol. 104, No. 13, pp. 4300-4307, 4294. print.
CODEN: BLOOAW. ISSN: 0006-4971.
DT Article
LA English
ED Entered STN: 16 Feb 2005
Last Updated on STN: 16 Feb 2005

L9 ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI A novel GATA-specific inhibitor (GSI) rescues anemia of chronic disease by oral administration.
AB The disorders associated with anemia of chronic disease (ACD) are characterized by the production of interleukin-1beta (IL-Ibeta) and tumor necrosis factor-alpha (TNF-alpha), which increase the binding activity of GATA-2 and NF-kappaB and inhibit production of **erythropoietin** (Epo). Because Epo promoter activity is negatively regulated by GATA binding, GATA-2 may be responsible for impaired Epo synthesis in inflammatory disease in vivo. On the other hand, we found that NG-monomethyl L-arginine (L-NMMA), which is increased in patients with chronic renal failure, inhibits NO and cGMP production, increases the binding activity of GATA and mRNA expression, and inhibits Epo promoter activity. Therefore, one common pathogenesis of ACD and anemia of renal disease appears to be via the stimulation of GATA binding activity. We have shown that intraperitoneal injection of **K-7174**, a GATA-specific inhibitor, improves Epo production which had been inhibited by IL-1beta and TNF-alpha. In this study, a novel GSI, which has a 100-fold higher affinity than **K-7174**, was examined to further improve Epo production that had been inhibited by IL-1beta and TNF-alpha. The addition of 100 nM GSI rescued the inhibition of Epo protein production and promoter activity induced by IL-1beta and TNF-alpha, respectively. Electrophoretic mobility shift assays revealed that the addition of GSI decreased GATA binding activity, which was increased with the addition of IL-1beta and TNF-alpha. Furthermore, intraperitoneal injection of mice with IL-1beta or TNF-alpha decreased Epo levels, reticulocyte counts, hematocrits (Hts), hemoglobins (Hbs), the numbers of CFU-E from spleen and bone marrow, and the number of CD71+/Ter119+ cells from the spleen. However, oral administration of GSI reversed these effetcs. These results raise the possibility of using GSI as a novel drug for treating ACD by oral administration.
AN 2004:150875 BIOSIS
DN PREV200400147180
TI A novel GATA-specific inhibitor (GSI) rescues anemia of chronic disease by oral administration.
AU Imagawa, Shigehiko [Reprint Author]; Nakano, Yoko [Reprint Author]; Obara, Naoshi [Reprint Author]; Suzuki, Norio; Nagasawa, Toshiro [Reprint Author]; Yamamoto, Masayuki
CS Division of Hematology, Institution of Clinical Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan
SO Blood, (November 16 2003) Vol. 102, No. 11, pp. 510a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004

L9 ANSWER 5 OF 5 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI A GATA-specific inhibitor (**K-7174**) rescues anemia induced by IL-1beta, TNF-alpha, or L-NMMA.
AN 2003:448450 BIOSIS
DN PREV200300448450

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TI A GATA-specific inhibitor (**K-7174**) rescues anemia induced by IL-1beta, TNF-alpha, or L-NMMA.
AU Imagawa, Shigehiko [Reprint Author]; Nakano, Yoko; Obara, Naoshi; Suzuki, Norio; Doi, Takeshi; Kodama, Tatsuhiko; Nagasawa, Toshiro; Yamamoto, Masayuki
CS Division of Hematology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Ibaraki, 305-8575, Japan
simigawa@md.tsukuba.ac.jp
SO FASEB Journal, (September 2003) Vol. 17, No. 12, pp. 1742-1744. print.
ISSN: 0892-6638 (ISSN print).
DT Article
LA English
ED Entered STN: 1 Oct 2003
Last Updated on STN: 1 Oct 2003

=> s L8 and py<2003
1 FILES SEARCHED...
L10 3 L8 AND PY<2003

=> d 1-3 ti abs bib

L10 ANSWER 1 OF 3 MEDLINE on STN
TI A novel cell adhesion inhibitor, **K-7174**, reduces the endothelial VCAM-1 induction by inflammatory cytokines, acting through the regulation of **GATA.**
AB A novel inhibitor for the adhesion of monocytes to cytokine-stimulated endothelial cells, **K-7174**, was selected by an assay system using the cultured human monocytic cells and human endothelial cells. **K-7174** inhibited the expression of vascular cell adhesion molecule-1 (VCAM-1) induced by either tumor necrosis factor alpha or interleukin-1beta, without affecting the induction of intercellular adhesion molecule-1 or E-selectin. **K-7174** had no effect on the stability of VCAM-1 mRNA. Electrophoretic mobility shift assay revealed that its inhibitory effect on VCAM-1 induction was mediated by an effect on the binding to the **GATA** motifs in the VCAM-1 gene promoter region. **K-7174** did not influence the binding to any of the following binding motifs: octamer binding protein, AP-1, SP-1, ets, NFkappaB, or interferon regulatory factor. These results suggest that the regulation of **GATA** binding may become a new target for anti-inflammatory drug development, acting through a mechanism independent from NFkappaB activity.

AN 2000294848 MEDLINE
DN PubMed ID: 10833420
TI A novel cell adhesion inhibitor, **K-7174**, reduces the endothelial VCAM-1 induction by inflammatory cytokines, acting through the regulation of **GATA.**
AU Umetani M; Nakao H; Doi T; Iwasaki A; Ohtaka M; Nagoya T; Mataki C; Hamakubo T; Kodama T
CS Department of Molecular Biology and Medicine, University of Tokyo, Japan.
SO Biochemical and biophysical research communications, **(2000 Jun 7)** Vol. 272, No. 2, pp. 370-4.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200007
ED Entered STN: 20000720
Last Updated on STN: 20000720
Entered Medline: 20000710

Eryhtropoietin production potentiator

L10 ANSWER 2 OF 3 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI **GATA**-Specific Inhibitor (**K-7174**) Rescues
Anemia Induced by IL-1beta, TNF-alpha or L-NMMA.
AB Disorders associated with the anemia of chronic disease (ACD) are characterized by the production of IL-1beta and TNF-alpha which inhibit production of Epo. Recently Jelkmann et al. reported that IL-1beta and TNF-alpha increase the binding activity of **GATA**-2, and inhibit Epo gene expression. This is because Epo gene expression is negatively regulated by the binding of **GATA** to the **GATA** site of Epo promoter. Thus, **GATA**-2 seems to be involved in the suppression of Epo gene expression by IL-1beta and TNF-alpha in vitro, and may be responsible for impaired Epo synthesis in inflammatory disease in vivo. On the other hand, we found that NG-monomethyl L-arginine (L-NMMA) which increased in patients with chronic renal failure, inhibits NOcntdotcGMP production, increases the binding activity of **GATA** and mRNA expression, and inhibits Epo promoter activity. In this study, we examined the ability of **K-7174** (a **GATA** -specific inhibitor) to improve Epo production when Epo production was inhibited by IL-1beta, TNF-alpha or L-NMMA. Hypoxia induced Epo protein from Hep3B cells, resulting in an activity of 1616 mU/mg protein. In the presence of 15 U/mL IL-1beta, 220 U/mL TNF-alpha, the increase in Epo protein by hypoxia was only 751 and 713 mU/mg protein, respectively. Addition of 10mu M **K-7174** increased Epo protein to 2042 mU/mg protein and rescued the inhibition of Epo protein by IL-1beta, TNF-alpha to 1168, 1072 mU/mg protein, respectively. Hypoxia induced Epo promoter activity 34 fold. In the presence of 15 U/mL IL-1beta, 220 U/mL TNF-alpha or 10-3 M L-NMMA, the increase in promoter activity by hypoxia was only 20, 21 and 17 fold, respectively. 10mu M **K-7174** increased promoter activity to 40 fold. Addition of 10mu M **K-7174** rescued the inhibition of promoter activity by IL-1beta, TNF-alpha or L-NMMA to 43, 50 or 32 fold, respectively. An electrophoretic mobility shift assay revealed that the addition of **K-7174** decreased the **GATA** binding activity which was increased by the addition of IL-1beta, TNF-alpha or L-NMMA, respectively. ICR mice were divided into 5 groups (A-E). The A group was injected with 100mu L PBS on days 0-5. The B group was injected with 1.6 X 104 U IL-1beta on days 0-2. The C group was injected with 5 X 104 U TNF-alpha on days 0-2. The D group was injected with 1.6 X 104 U IL-1beta on days 0-2, and 30mg/kg **K-7174** on days 0-5. The E group was injected with 5 X 104 U TNF-alpha on days 0-2, and 30mg/kg **K-7174** on days 0-5. Blood samples were obtained from the orbital vein on days 0, 2, and 5. The hematocrit (Ht) of the control was 47.5% on day 0 and 43.9% on day 5. Injection of IL-1beta, TNF-alpha decreased the Hts from 48.7%, 48.7% on day 0 to 38.7%, 37.1% on day 5, respectively. However, **K-7174** rescued the inhibition of Ht by IL-1beta from 49.4% on day 0 to 47.0% on day 5, and rescued the inhibition of Ht by TNF-alpha from 48.5% on day 0 to 43.1% on day 5, respectively. These results raise the possibility of using **K-7174** as a novel drug for improving anemia.
AN 2003:356717 BIOSIS
DN PREV200300356717
TI **GATA**-Specific Inhibitor (**K-7174**) Rescues
Anemia Induced by IL-1beta, TNF-alpha or L-NMMA.
AU Imagawa, Shigehiko [Reprint Author]; Nakano, Yoko [Reprint Author]; Obara, Naoshi [Reprint Author]; Suzuki, Norio [Reprint Author]; Doi, Takeshi [Reprint Author]; Kodama, Tatsuhiko [Reprint Author]; Yamamoto, Masayuki [Reprint Author]; Nagasawa, Toshiro [Reprint Author]
CS Division of Hematology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan
SO Blood, (**November 16 2002**) Vol. 100, No. 11, pp. Abstract No. 2583. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of

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Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 6 Aug 2003
Last Updated on STN: 6 Aug 2003

L10 ANSWER 3 OF 3 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI A novel cell adhesion inhibitor, **K-7174**, reduces the endothelial VCAM-1 induction by inflammatory cytokines, acting through the regulation of **GATA**.
AB A novel inhibitor for the adhesion of monocytes to cytokine-stimulated endothelial cells, **K-7174**, was selected by an assay system using the cultured human monocytic cells and human endothelial cells. **K-7174** inhibited the expression of vascular cell adhesion molecule-1 (VCAM-1) induced by either tumor necrosis factor alpha or interleukin-1beta, without affecting the induction of intercellular adhesion molecule-1 or E-selectin. **K-7174** had no effect on the stability of VCAM-1 mRNA. Electrophoretic mobility shift assay revealed that its inhibitory effect on VCAM-1 induction was mediated by an effect on the binding to the **GATA** motifs in the VCAM-1 gene promoter region. **K-7174** did not influence the binding to any of the following binding motifs: octamer binding protein, AP-1, SP-1, ets, NFkappaB, or interferon regulatory factor. These results suggest that the regulation of **GATA** binding may become a new target for anti-inflammatory drug development, acting through a mechanism independent from NFkappaB activity.
AN 2000:347907 BIOSIS
DN PREV200000347907
TI A novel cell adhesion inhibitor, **K-7174**, reduces the endothelial VCAM-1 induction by inflammatory cytokines, acting through the regulation of **GATA**.
AU Umetani, Michihisa; Nakao, Hiroshi; Doi, Takeshi; Iwasaki, Akio; Ohtaka, Manami; Nagoya, Takao; Mataki, Chikage; Hamakubo, Takao; Kodama, Tatsuhiko [Reprint author]
CS Department of Molecular Biology and Medicine, University of Tokyo, 4-6-1 Komaba, Meguro, No. 35, RCAST, Tokyo, 153-0084, Japan
SO Biochemical and Biophysical Research Communications, (**June 7, 2000**) Vol. 272, No. 2, pp. 370-374. print.
CODEN: BBRCA9. ISSN: 0006-291X.
DT Article
LA English
ED Entered STN: 16 Aug 2000
Last Updated on STN: 7 Jan 2002

=> logoff
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	15.32	15.53

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NEWS 4	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS 5	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS 6	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS 7	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS 8	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS 9	JAN 30	Saved answer limit increased
NEWS 10	JAN 31	Monthly current-awareness alert (SDI) frequency added to TULSA
NEWS 11	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS 12	FEB 22	Status of current WO (PCT) information on STN
NEWS 13	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS 14	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS 15	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS 16	FEB 28	MEDLINE/LMEDLINE reload improves functionality
NEWS 17	FEB 28	TOXCENTER reloaded with enhancements
NEWS 18	FEB 28	REGISTRY/ZREGISTRY enhanced with more experimental spectral property data
NEWS 19	MAR 01	INSPEC reloaded and enhanced
NEWS 20	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS 21	MAR 08	X.25 communication option no longer available after June 2006
NEWS 22	MAR 22	EMBASE is now updated on a daily basis

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
http://download.cas.org/express/v8.0-Discover/

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Eryhtropoietin production potentiator

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FILE 'HOME' ENTERED AT 17:44:54 ON 27 MAR 2006

=> s 203721-89-5<chem>
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> file medline biosis
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.63	0.63

FILE 'MEDLINE' ENTERED AT 17:46:35 ON 27 MAR 2006

FILE 'BIOSIS' ENTERED AT 17:46:35 ON 27 MAR 2006
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=> s 203721-89-5<chem>
MISSING TERM AFTER -89-5<CHEM>
Operators must be followed by a search term, L-number, or query name.

=> file registry
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.26	1.89

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DICTIONARY FILE UPDATES: 26 MAR 2006 HIGHEST RN 878044-67-8

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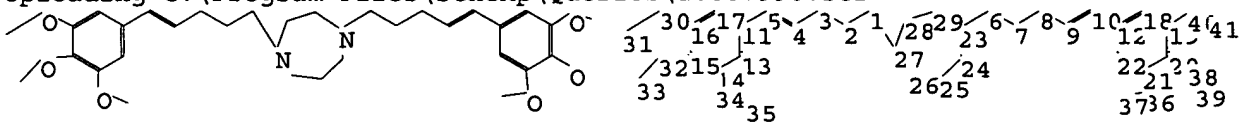


chain nodes :
30 31 32 33 34 35 36 37 38 39 40 41
ring nodes :
11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
ring/chain nodes :
1 2 3 4 5 6 7 8 9 10
chain bonds :
1-27 6-23 14-34 15-32 16-30 19-40 20-38 21-36 30-31 32-33 34-35 36-37
38-39 40-41
ring/chain bonds :
1-2 2-3 3-4 4-5 5-11 6-7 7-8 8-9 9-10 10-12
ring bonds :
11-13 11-17 12-18 12-22 13-14 14-15 15-16 16-17 18-19 19-20 20-21 21-22
23-24 23-29 24-25 25-26 26-27 27-28 28-29
exact/norm bonds :
1-2 1-27 2-3 3-4 4-5 5-11 6-7 6-23 7-8 8-9 9-10 10-12 14-34 15-32
16-30 19-40 20-38 21-36 23-24 23-29 24-25 25-26 26-27 27-28 28-29 30-31
32-33 34-35 36-37 38-39 40-41
normalized bonds :
11-13 11-17 12-18 12-22 13-14 14-15 15-16 16-17 18-19 19-20 20-21 21-22

Match level :
1:CLASS 2:CLASS 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLASS
10:CLASS 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom
19:Atom 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom
28:Atom 29:Atom 30:CLASS 31:CLASS 32:CLASS 33:CLASS 34:CLASS 35:CLASS
36:CLASS 37:CLASS 38:CLASS 39:CLASS 40:CLASS 41:CLASS

L1 STRUCTURE UPLOADED

=> s L1
SAMPLE SEARCH INITIATED 17:47:16 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 74 TO ITERATE

100.0% PROCESSED 74 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 964 TO 1996
PROJECTED ANSWERS: 2 TO 124

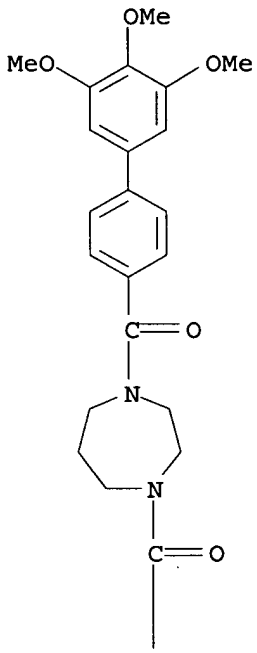
L2 2 SEA SSS SAM L1

=> d 1-2

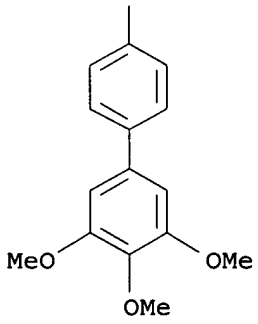
Eryhtropoietin production potentiator

L2 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2006 ACS on STN
RN 203721-89-5 REGISTRY
ED Entered STN: 07 Apr 1998
CN 1H-1,4-Diazepine, hexahydro-1,4-bis[(3',4',5'-trimethoxy[1,1'-biphenyl]-4-yl)carbonyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C37 H40 N2 O8
SR CA
LC STN Files: CA, CAPLUS, USPAT2, USPATFULL

PAGE 1-A



PAGE 2-A



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

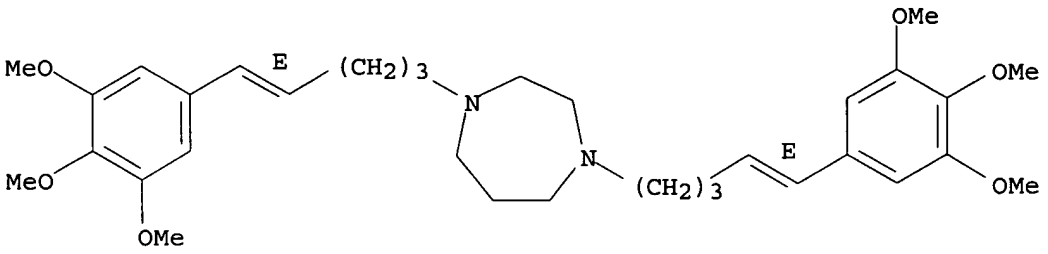
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2006 ACS on STN

Eryhtropoietin production potentiator

RN 191089-59-5 REGISTRY
ED Entered STN: 11 Jul 1997
CN 1H-1,4-Diazepine, hexahydro-1,4-bis[(4E)-5-(3,4,5-trimethoxyphenyl)-4-pentenyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-1,4-Diazepine, hexahydro-1,4-bis[5-(3,4,5-trimethoxyphenyl)-4-pentenyl]-, (E,E)-
OTHER NAMES:
CN K 7174
FS STEREOSEARCH
DR 286441-08-5
MF C33 H48 N2 O6
CI COM
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, PROUSDDR, SYNTHLINE, TOXCENTER, USPATFULL

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

6 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file medline biosis

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	4.68	6.57

FILE 'MEDLINE' ENTERED AT 17:47:50 ON 27 MAR 2006

FILE 'BIOSIS' ENTERED AT 17:47:50 ON 27 MAR 2006
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=> s L1<chem>
L-NUMBER SPECIFIED IS NOT AN ANSWER SET
The L-number answer set specified in the SmartSELECT search must contain one or more answers.

=> file caplus biosis

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.26	7.83

FILE 'CAPLUS' ENTERED AT 17:48:17 ON 27 MAR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'BIOSIS' ENTERED AT 17:48:17 ON 27 MAR 2006
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Eryhtropoietin production potentiator

=> s L1<chem>
L-NUMBER SPECIFIED IS NOT AN ANSWER SET
The L-number answer set specified in the SmartSELECT search must
contain one or more answers.

=> s L1 <chem>
L-NUMBER SPECIFIED IS NOT AN ANSWER SET
The L-number answer set specified in the SmartSELECT search must
contain one or more answers.

=> file medline biosis caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.33	9.16

FILE 'MEDLINE' ENTERED AT 17:48:37 ON 27 MAR 2006

FILE 'BIOSIS' ENTERED AT 17:48:37 ON 27 MAR 2006
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=> s L2<chem>

SmartSELECT INITIATED
New TRANSFER and ANALYZE Commands Now Available
See HELP TRANSFER and HELP ANALYZE for Details

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.72	10.88

FILE 'REGISTRY' ENTERED AT 17:48:42 ON 27 MAR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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SET SMARTSELECT ON
SET COMMAND COMPLETED

SEL L2 1- CHEM
L3 SEL L2 1- CHEM : 4 TERMS

SET SMARTSELECT OFF
SET COMMAND COMPLETED

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	11.29	22.17

FILE 'MEDLINE' ENTERED AT 17:48:42 ON 27 MAR 2006

FILE 'BIOSIS' ENTERED AT 17:48:42 ON 27 MAR 2006
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FILE 'CAPLUS' ENTERED AT 17:48:42 ON 27 MAR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

Eryhtropoietin production potentiator

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

S L3
L4 17 L3

=> rem dup L4
DUP IS NOT VALID HERE
The DELETE command is used to remove various items stored by the system.

To delete a saved query, saved answer set, saved L-number list, SDI request, batch request, mailing list, or user-defined cluster, format, or search field, enter the name. The name may include ? for left, right, or simultaneous left and right truncation.

Examples:

```
DELETE BIO?/Q           - delete query names starting with BIO
DELETE ?DRUG/A          - delete answer set names ending with DRUG
DELETE ?ELEC?/L         - delete L-number lists containing ELEC
DELETE ANTICOAG/S       - delete SDI request
DELETE ENZYME/B         - delete batch request
DELETE .MYCLUSTER       - delete user-defined cluster
DELETE .MYFORMAT        - delete user-defined display format
DELETE .MYFIELD         - delete user-defined search field
DELETE NAMELIST MYLIST - delete mailing list
```

To delete an ordered document or an offline print, enter its number.

Examples:

```
DELETE P123001C         - delete print request
DELETE D134002C         - delete document order request
```

To delete an individual L-number or range of L-numbers, enter the L-number or L-number range. You may also enter DELETE LAST followed by a number, n, to delete the last n L-numbers. RENUMBER or NORENUMBER may also be explicitly specified to override the value of SET RENUMBER.

Examples:

```
DELETE L21              - delete a single L-number
DELETE L3-L6            - delete a range of L-numbers
DELETE LAST 4           - delete the last 4 L-numbers
DELETE L33-             - delete L33 and any higher L-number
DELETE -L55             - delete L55 and any lower L-number
DELETE L2-L6 RENUMBER - delete a range of L-numbers and
                          renumber remaining L-numbers
DELETE RENUMBER         - renumber L-numbers after deletion of
                          intermediate L-numbers
```

Entire sets of saved items, SDI requests, batch requests, user-defined items, or E-numbers can be deleted.

Examples:

```
DELETE SAVED/Q - delete all saved queries
DELETE SAVED/A - delete all saved answer sets
DELETE SAVED/L - delete all saved L-number lists
DELETE SAVED   - delete all saved queries, answer sets,
```

Eryhtropoietin production potentiator

```
                    and L-number lists
  DELETE SAVED/S - delete all SDI requests
  DELETE SAVED/B - delete all batch requests
  DELETE CLUSTER - delete all user-defined clusters
  DELETE FORMAT  - delete all user-defined display formats
  DELETE FIELD   - delete all user-defined search fields
  DELETE SELECT  - delete all E-numbers
  DELETE HISTORY - delete all L-numbers and restart the
                   session at L1

To delete an entire multifile SDI request, enter DELETE and
the name of the request.  To delete a component from the
multifile SDI, enter DELETE and the name of the component.

=> dup rem L4
PROCESSING COMPLETED FOR L4
L5            11 DUP REM L4 (6 DUPLICATES REMOVED)

=> d L5 1-11 ti abs

L5   ANSWER 1 OF 11     MEDLINE on STN                    DUPLICATE 1
TI   Oral administration of K-11706 inhibits GATA binding activity, enhances
     hypoxia-inducible factor 1 binding activity, and restores indicators in an
     in vivo mouse model of anemia of chronic disease.
AB   Erythropoietin (Epo) gene expression is under the control of
     hypoxia-inducible factor 1 (HIF-1), and is negatively regulated by GATA.
     Interleukin 1beta (IL-1beta) and tumor necrosis factor alpha (TNF-alpha),
     which increase the binding activity of GATA and inhibit Epo promoter
     activity, are increased in patients with anemia of chronic disease (ACD).
     We previously demonstrated the ability of K-7174 (a
     GATA-specific inhibitor), when injected intraperitoneally, to improve Epo
     production that had been inhibited by IL-1beta or TNF-alpha treatment.  In
     the present study, we examined the ability of both K-11706, which inhibits
     GATA and enhances HIF-1 binding activity, and K-13144, which has no effect
     on GATA or HIF-1 binding activity, to improve Epo production following
     inhibition by IL-1beta or TNF-alpha in Hep3B cells in vitro and in an in
     vivo mouse assay.  Oral administration of K-11706 reversed the decreases
     in hemoglobin and serum Epo concentrations, reticulocyte counts, and
     numbers of erythroid colony-forming units (CFU-Es) induced by IL-1beta or
     TNF-alpha.  These results raise the possibility of using orally
     administered K-11706 for treating patients with ACD.

L5   ANSWER 2 OF 11     MEDLINE on STN                    DUPLICATE 2
TI   A GATA-specific inhibitor (K-7174) rescues anemia
     induced by IL-1beta, TNF-alpha, or L-NMMA.
AB   Interleukin-1beta (IL-1beta), tumor necrosis factor-alpha (TNF-alpha), or
     N(G)-monomethyl-L-arginine (L-NMMA) are increased in patients with chronic
     disease-related anemia.  They increase the binding activity of GATA and
     inhibit erythropoietin (Epo) promoter activity.  In this study, we
     examined the ability of K-7174 (a GATA-specific
     inhibitor) to improve Epo production when inhibited by treatment with
     IL-1beta, TNF-alpha, or L-NMMA.  Epo protein production and promoter
     activity were induced in Hep3B cells with 1% O2.  However, 15 U/ml
     IL-1beta, 220 U/ml TNF-alpha, or 10(-3) M L-NMMA inhibited Epo protein
     production and promoter activity, respectively.  Addition of 10 microM
     K-7174 rescued these inhibitions of Epo protein
     production and promoter activity induced by IL-1beta, TNF-alpha, or
     L-NMMA, respectively.  Electrophoretic mobility shift assays revealed that
     addition of K-7174 decreased GATA binding activity,
     which was increased with the addition of IL-1beta, TNF-alpha, or L-NMMA.
     Furthermore, intraperitoneal injection of mice with IL-1beta or TNF-alpha
     decreased the hemoglobin concentrations and reticulocyte counts.  However,
     the addition of K-7174 reversed these effects.  These
```

results raise the possibility of using **K-7174** as therapy to treat anemia.

L5 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
TI Trial of novel drug for secondary anemia from chronic disease
AB The GATA specific blocker **K 7174** inhibited IL-1β and TNF-α-induced GATA binding activity and increased erythropoietin formation in Hep3B cells. The results indicated that **K 7174** may be useful for treatment of secondary anemia from chronic disease.

L5 ANSWER 4 OF 11 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI A novel GATA-specific inhibitor (GSI) rescues anemia of chronic disease by oral administration.
AB The disorders associated with anemia of chronic disease (ACD) are characterized by the production of interleukin-1beta (IL-Ibeta) and tumor necrosis factor-alpha (TNF-alpha), which increase the binding activity of GATA-2 and NF-kappaB and inhibit production of erythropoietin (Epo). Because Epo promoter activity is negatively regulated by GATA binding, GATA-2 may be responsible for impaired Epo synthesis in inflammatory disease in vivo. On the other hand, we found that NG-monomethyl L-arginine (L-NMMA), which is increased in patients with chronic renal failure, inhibits NO and cGMP production, increases the binding activity of GATA and mRNA expression, and inhibits Epo promoter activity. Therefore, one common pathogenesis of ACD and anemia of renal disease appears to be via the stimulation of GATA binding activity. We have shown that intraperitoneal injection of **K-7174**, a GATA-specific inhibitor, improves Epo production which had been inhibited by IL-1beta and TNF-alpha. In this study, a novel GSI, which has a 100-fold higher affinity than **K-7174**, was examined to further improve Epo production that had been inhibited by IL-1beta and TNF-alpha. The addition of 100 nM GSI rescued the inhibition of Epo protein production and promoter activity induced by IL-1beta and TNF-alpha, respectively. Electrophoretic mobility shift assays revealed that the addition of GSI decreased GATA binding activity, which was increased with the addition of IL-1beta and TNF-alpha. Furthermore, intraperitoneal injection of mice with IL-1beta or TNF-alpha decreased Epo levels, reticulocyte counts, hematocrits (Hts), hemoglobins (Hbs), the numbers of CFU-E from spleen and bone marrow, and the number of CD71+/Ter119+ cells from the spleen. However, oral administration of GSI reversed these effetcs. These results raise the possibility of using GSI as a novel drug for treating ACD by oral administration.

L5 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
TI Novel erythropoietin-stimulating drug (**K-7174**): Trial for renal anemia
AB **K-7174** stimulated erythropoietin activity in HEP3B by inhibiting GATA transcription factor in vitro. The results are discussed with regards to treatment of renal anemia by **K-7174**.

L5 ANSWER 6 OF 11 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI A NOVEL CELL ADHESION INHIBITOR, **K - 7174**, REDUCES LYMPHOCYTE INFILTRATION AND INCREASES TEAR PRODUCTION IN SJoGREN'S SYNDROME MODEL MOUSE.
AB Purpose: To investigate the effect of a novel cell adhesion inhibitor, **K-7174**, for the improvement of dry eye in Sjogrens model mouse. Methods: A total of 30 NFS/sld thymectomized mice, 4 weeks after birth, were treated by oral administration (N=15, vehicle, 10m/kg and 30mg/kg) or topical application (N=15, vehicle, 0.8mg/ml, and 2.4mg/ml) of **K-7174** for 10 weeks. Tear secretion was measured by cotton thread and lymphocyte infiltration in the lacrimal glands were graded. Gene expression of lacrimal glands, with and without treatment, were assayed by gene-chip analysis (Affymetrix). Results: Tear secretion

increased to 0.175 +/- 0.062 (10mg/kg) and 0.198 +/- 0.039 (30mg/kg) in oral administered groups compared to 0.092 +/- 0.030 mm/min/g (vehicle). Similar results were obtained in the topical treatment group. Lymphocyte infiltration grades decreased to 0.63 +/- 0.31 (10mg/kg) and 0.0 +/- 0.0 (30mg/kg) compared to 3.71 +/- 0.41 (vehicle). Similar results were obtained in topical administered groups (0.6+/-0.48 in 2.4mg/ml, 0.6 +/- 0.48 in 0.8mg/ml and 2.6+/- 0.9 in vehicle). Fractalkine, a newly discovered lymphocyte trafficking chemokine, was found to be suppressed dramatically in the lacrimal gland of treated mice among the 11 suppressed genes. Conclusion: Both systemic and topical application of **K-7174** increases tear secretion and decreases lymphocyte infiltration of lacrimal glands in NFS/sld thymectomized mice. **K-7174** could possibly be a new drug for the control of inflammation of Sjogren's syndrome and Fractalkine may one of the target molecules in this treatment mechanism.

L5 ANSWER 7 OF 11 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

TI GATA-Specific Inhibitor (**K-7174**) Rescues Anemia Induced by IL-1beta, TNF-alpha or L-NMMA.

AB Disorders associated with the anemia of chronic disease (ACD) are characterized by the production of IL-1beta and TNF-alpha which inhibit production of Epo. Recently Jelkmann et al. reported that IL-1beta and TNF-alpha increase the binding activity of GATA-2, and inhibit Epo gene expression. This is because Epo gene expression is negatively regulated by the binding of GATA to the GATA site of Epo promoter. Thus, GATA-2 seems to be involved in the suppression of Epo gene expression by IL-1beta and TNF-alpha in vitro, and may be responsible for impaired Epo synthesis in inflammatory disease in vivo. On the other hand, we found that NG-monomethyl L-arginine (L-NMMA) which increased in patients with chronic renal failure, inhibits NOcntdotcGMP production, increases the binding activity of GATA and mRNA expression, and inhibits Epo promoter activity. In this study, we examined the ability of **K-7174** (a GATA-specific inhibitor) to improve Epo production when Epo production was inhibited by IL-1beta, TNF-alpha or L-NMMA. Hypoxia induced Epo protein from Hep3B cells, resulting in an activity of 1616 mU/mg protein. In the presence of 15 U/mL IL-1beta, 220 U/mL TNF-alpha, the increase in Epo protein by hypoxia was only 751 and 713 mU/mg protein, respectively. Addition of 10mu M **K-7174** increased Epo protein to 2042 mU/mg protein and rescued the inhibition of Epo protein by IL-1beta, TNF-alpha to 1168, 1072 mU/mg protein, respectively. Hypoxia induced Epo promoter activity 34 fold. In the presence of 15 U/mL IL-1beta, 220 U/mL TNF-alpha or 10-3 M L-NMMA, the increase in promoter activity by hypoxia was only 20, 21 and 17 fold, respectively. 10mu M **K-7174** increased promoter activity to 40 fold. Addition of 10mu M **K-7174** rescued the inhibition of promoter activity by IL-1beta, TNF-alpha or L-NMMA to 43, 50 or 32 fold, respectively. An electrophoretic mobility shift assay revealed that the addition of **K-7174** decreased the GATA binding activity which was increased by the addition of IL-1beta, TNF-alpha or L-NMMA, respectively. ICR mice were divided into 5 groups (A-E). The A group was injected with 100mu L PBS on days 0-5. The B group was injected with 1.6 X 104 U IL-1beta on days 0-2. The C group was injected with 5 X 104 U TNF-alpha on days 0-2. The D group was injected with 1.6 X 104 U IL-1beta on days 0-2, and 30mg/kg **K-7174** on days 0-5. The E group was injected with 5 X 104 U TNF-alpha on days 0-2, and 30mg/kg **K-7174** on days 0-5. Blood samples were obtained from the orbital vein on days 0, 2, and 5. The hematocrit (Ht) of the control was 47.5% on day 0 and 43.9% on day 5. Injection of IL-1beta, TNF-alpha decreased the Hts from 48.7%, 48.7% on day 0 to 38.7%, 37.1% on day 5, respectively. However, **K-7174** rescued the inhibition of Ht by IL-1beta from 49.4% on day 0 to 47.0% on day 5, and rescued the inhibition of Ht by TNF-alpha from 48.5% on day 0 to 43.1% on day 5, respectively. These results raise the possibility of using **K-7174** as

Eryhtropoietin production potentiator

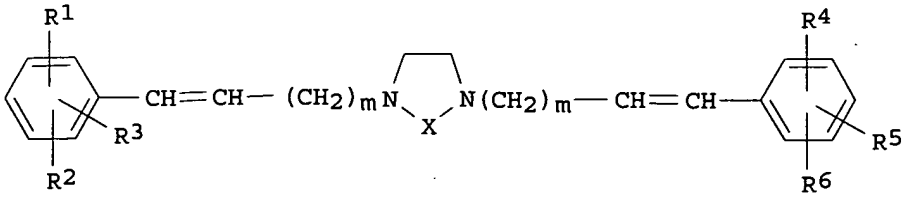
a novel drug for improving anemia.

L5 ANSWER 8 OF 11 MEDLINE on STN DUPLICATE 3
TI A novel cell adhesion inhibitor, **K-7174**, reduces the endothelial VCAM-1 induction by inflammatory cytokines, acting through the regulation of GATA.
AB A novel inhibitor for the adhesion of monocytes to cytokine-stimulated endothelial cells, **K-7174**, was selected by an assay system using the cultured human monocytic cells and human endothelial cells. **K-7174** inhibited the expression of vascular cell adhesion molecule-1 (VCAM-1) induced by either tumor necrosis factor alpha or interleukin-1beta, without affecting the induction of intercellular adhesion molecule-1 or E-selectin. **K-7174** had no effect on the stability of VCAM-1 mRNA. Electrophoretic mobility shift assay revealed that its inhibitory effect on VCAM-1 induction was mediated by an effect on the binding to the GATA motifs in the VCAM-1 gene promoter region. **K-7174** did not influence the binding to any of the following binding motifs: octamer binding protein, AP-1, SP-1, ets, NFkappaB, or interferon regulatory factor. These results suggest that the regulation of GATA binding may become a new target for anti-inflammatory drug development, acting through a mechanism independent from NFkappaB activity.

L5 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
TI Preparation of diamide compounds as IgE production inhibitors
AB Diamide derivs. ABCOWCOBA [A represents optionally substituted Ph, etc.; B represents CH:CH, C.tplbond.C, phenylene, etc.; and W represents 1,4,8-triazabicyclo[4,4,0]decane, etc.] are prepared The title compds. are useful as antiallergic agents, etc. Thus, 1,4-bis[5-phenylpenta-(2E,4E)-dienoyl]hexahydro-1,4-diazepine at 10-5 M gave 100% inhibition of IgE production in B cells.

L5 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
TI An inhibitor of VCAM-1 expression and its implication as a novel treatment of inflammatory diseases
AB To evaluate endothelial-leukocyte adhesion, we developed an adhesion technique using human umbilical vein endothelial cells (HUVECs) and U-937 cells. This technique clarified that ICAM-1 and VCAM-1 were primarily responsible for this adhesion. Using this technique, we found a low mol. weight compound that potently inhibits the adhesion through specifically suppressing the expression of VCAM-1 of HUVECs. When orally administered to mice, this compound also diminished the increase in paw thickness and in anti-bovine type II collagen (anti-BII) antibodies in mouse collagen-induced arthritis.

L5 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
TI Preparation of N,N'-bis(aralkenyl)piperazine and -homopiperazines as inhibitors of cellular adhesion and infiltration.
GI



I

AB Title compds. (I; X = (CH2)n; R1-R6 = H, halo, OH, alkyl, alkoxy; m = 1-3;

Eryhtropoietin production potentiator

n = 2, 3), were prepared Thus, (E)-5-(3,4,5-trimethoxyphenyl)-4-pentenyl bromide, homopiperazine, K2CO3, KI, and DMF were heated at 100° to give N,N'-bis[(E)-(3,4,5-trimethoxyphenyl)-4-pentenyl]homopiperazine (II). II at 30 mg/kg i.p. in guinea pigs reduced infiltration of trachea by eosinocytes from 204.5 cells/mm to 122.2 cells/mm. II tablet and capsule formulations are given.

```
=> s L5 and py<2003
   1 FILES SEARCHED...
L6            5 L5 AND PY<2003

=> d L6 1-5 ti abs bib

L6   ANSWER 1 OF 5     MEDLINE on STN
TI   A novel cell adhesion inhibitor, K-7174, reduces the
     endothelial VCAM-1 induction by inflammatory cytokines, acting through the
     regulation of GATA.
AB   A novel inhibitor for the adhesion of monocytes to cytokine-stimulated
     endothelial cells, K-7174, was selected by an assay
     system using the cultured human monocytic cells and human endothelial
     cells. K-7174 inhibited the expression of vascular
     cell adhesion molecule-1 (VCAM-1) induced by either tumor necrosis factor
     alpha or interleukin-1beta, without affecting the induction of
     intercellular adhesion molecule-1 or E-selectin. K-7174
     had no effect on the stability of VCAM-1 mRNA. Electrophoretic mobility
     shift assay revealed that its inhibitory effect on VCAM-1 induction was
     mediated by an effect on the binding to the GATA motifs in the VCAM-1 gene
     promoter region. K-7174 did not influence the binding
     to any of the following binding motifs: octamer binding protein, AP-1,
     SP-1, ets, NFkappaB, or interferon regulatory factor. These results
     suggest that the regulation of GATA binding may become a new target for
     anti-inflammatory drug development, acting through a mechanism independent
     from NFkappaB activity.
     Copyright 2000 Academic Press.
AN   2000294848     MEDLINE
DN   PubMed ID: 10833420
TI   A novel cell adhesion inhibitor, K-7174, reduces the
     endothelial VCAM-1 induction by inflammatory cytokines, acting through the
     regulation of GATA.
AU   Umetani M; Nakao H; Doi T; Iwasaki A; Ohtaka M; Nagoya T; Mataki C;
     Hamakubo T; Kodama T
CS   Department of Molecular Biology and Medicine, University of Tokyo, Japan.
SO   Biochemical and biophysical research communications, (2000 Jun 7)
     Vol. 272, No. 2, pp. 370-4.
     Journal code: 0372516. ISSN: 0006-291X.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200007
ED   Entered STN: 20000720
     Last Updated on STN: 20000720
     Entered Medline: 20000710

L6   ANSWER 2 OF 5  BIOSIS  COPYRIGHT (c) 2006 The Thomson Corporation  on STN
TI   GATA-Specific Inhibitor (K-7174) Rescues Anemia
     Induced by IL-1beta, TNF-alpha or L-NMMA.
AB   Disorders associated with the anemia of chronic disease (ACD) are
     characterized by the production of IL-1beta and TNF-alpha which inhibit
     production of Epo. Recently Jelkmann et al. reported that IL-1beta and
     TNF-alpha increase the binding activity of GATA-2, and inhibit Epo gene
     expression. This is because Epo gene expression is negatively regulated
```

by the binding of GATA to the GATA site of Epo promoter. Thus, GATA-2 seems to be involved in the suppression of Epo gene expression by IL-1beta and TNF-alpha in vitro, and may be responsible for impaired Epo synthesis in inflammatory disease in vivo. On the other hand, we found that NG-monomethyl L-arginine (L-NMMA) which increased in patients with chronic renal failure, inhibits NOcntdotcGMP production, increases the binding activity of GATA and mRNA expression, and inhibits Epo promoter activity. In this study, we examined the ability of **K-7174** (a GATA-specific inhibitor) to improve Epo production when Epo production was inhibited by IL-1beta, TNF-alpha or L-NMMA. Hypoxia induced Epo protein from Hep3B cells, resulting in an activity of 1616 mU/mg protein. In the presence of 15 U/mL IL-1beta, 220 U/mL TNF-alpha, the increase in Epo protein by hypoxia was only 751 and 713 mU/mg protein, respectively. Addition of 10mu M **K-7174** increased Epo protein to 2042 mU/mg protein and rescued the inhibition of Epo protein by IL-1beta, TNF-alpha to 1168, 1072 mU/mg protein, respectively. Hypoxia induced Epo promoter activity 34 fold. In the presence of 15 U/mL IL-1beta, 220 U/mL TNF-alpha or 10-3 M L-NMMA, the increase in promoter activity by hypoxia was only 20, 21 and 17 fold, respectively. 10mu M **K-7174** increased promoter activity to 40 fold. Addition of 10mu M **K-7174** rescued the inhibition of promoter activity by IL-1beta, TNF-alpha or L-NMMA to 43, 50 or 32 fold, respectively. An electrophoretic mobility shift assay revealed that the addition of **K-7174** decreased the GATA binding activity which was increased by the addition of IL-1beta, TNF-alpha or L-NMMA, respectively. ICR mice were divided into 5 groups (A-E). The A group was injected with 100mu L PBS on days 0-5. The B group was injected with 1.6 X 104 U IL-1beta on days 0-2. The C group was injected with 5 X 104 U TNF-alpha on days 0-2. The D group was injected with 1.6 X 104 U IL-1beta on days 0-2, and 30mg/kg **K-7174** on days 0-5. The E group was injected with 5 X 104 U TNF-alpha on days 0-2, and 30mg/kg **K-7174** on days 0-5. Blood samples were obtained from the orbital vein on days 0, 2, and 5. The hematocrit (Ht) of the control was 47.5% on day 0 and 43.9% on day 5. Injection of IL-1beta, TNF-alpha decreased the Hts from 48.7%, 48.7% on day 0 to 38.7%, 37.1% on day 5, respectively. However, **K-7174** rescued the inhibition of Ht by IL-1beta from 49.4% on day 0 to 47.0% on day 5, and rescued the inhibition of Ht by TNF-alpha from 48.5% on day 0 to 43.1% on day 5, respectively. These results raise the possibility of using **K-7174** as a novel drug for improving anemia.

AN 2003:356717 BIOSIS
DN PREV200300356717
TI GATA-Specific Inhibitor (**K-7174**) Rescues Anemia Induced by IL-1beta, TNF-alpha or L-NMMA.
AU Imagawa, Shigehiko [Reprint Author]; Nakano, Yoko [Reprint Author]; Obara, Naoshi [Reprint Author]; Suzuki, Norio [Reprint Author]; Doi, Takeshi [Reprint Author]; Kodama, Tatsuhiko [Reprint Author]; Yamamoto, Masayuki [Reprint Author]; Nagasawa, Toshiro [Reprint Author]
CS Division of Hematology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan
SO Blood, (**November 16 2002**) Vol. 100, No. 11, pp. Abstract No. 2583. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 6 Aug 2003
Last Updated on STN: 6 Aug 2003

Eryhtropoietin production potentiator

L6 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
TI An inhibitor of VCAM-1 expression and its implication as a novel treatment of inflammatory diseases
AB To evaluate endothelial-leukocyte adhesion, we developed an adhesion technique using human umbilical vein endothelial cells (HUVECs) and U-937 cells. This technique clarified that ICAM-1 and VCAM-1 were primarily responsible for this adhesion. Using this technique, we found a low mol. weight compound that potently inhibits the adhesion through specifically suppressing the expression of VCAM-1 of HUVECs. When orally administered to mice, this compound also diminished the increase in paw thickness and in anti-bovine type II collagen (anti-BII) antibodies in mouse collagen-induced arthritis.
AN 2000:228798 CAPLUS
DN 133:129534
TI An inhibitor of VCAM-1 expression and its implication as a novel treatment of inflammatory diseases
AU Nakao, Hiroshi; Doi, Takeshi; Suda, Makoto; Umetani, Michihisa; Ohtaka, Manami; Shiratsuchi, Masami; Kodama, Tatsuhiko
CS Department of Cell Biology, Kowa Research Institute, Ibaraki, 305-0856, Japan
SO Journal of Atherosclerosis and Thrombosis (**1998**), 4(4), 149-155
CODEN: JATHEH; ISSN: 1340-3478
PB Japan Atherosclerosis Society
DT Journal
LA English
RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
TI Preparation of diamide compounds as IgE production inhibitors
AB Diamide derivs. ABCOWCOBA [A represents optionally substituted Ph, etc.; B represents CH:CH, C.tplbond.C, phenylene, etc.; and W represents 1,4,8-triazabicyclo[4,4,0]decane, etc.] are prepared The title compds. are useful as antiallergic agents, etc. Thus, 1,4-bis[5-phenylpenta-(2E,4E)-dienoyl]hexahydro-1,4-diazepine at 10-5 M gave 100% inhibition of IgE production in B cells.
AN 1998:147312 CAPLUS
DN 128:192678
TI Preparation of diamide compounds as IgE production inhibitors
IN Ishiwata, Hiroyuki; Kabeya, Mototsugu; Shigyo, Hiromichi; Shiratsuchi, Masami; Hattori, Yukio; Nakao, Hiroshi; Nagoya, Takao; Sato, Seiichi; Oda, Soichi; et al.
PA Kowa Co., Ltd., Japan
SO PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

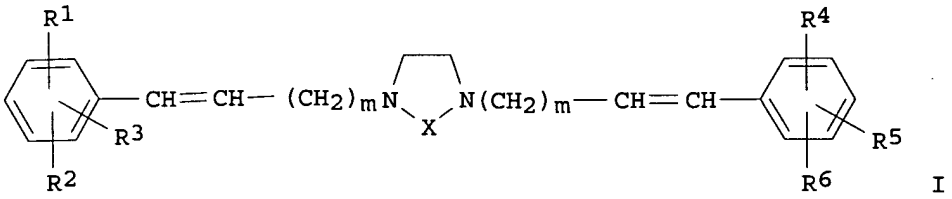
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9807702	A1	19980226	WO 1997-JP2882	19970820 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9738668	A1	19980306	AU 1997-38668	19970820 <--
EP 926138	A1	19990630	EP 1997-935832	19970820 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

Eryhtropoietin production potentiator

	US 6340682	B1	20020122	US 1999-147711	19990223 <--
	US 2002042414	A1	20020411	US 2001-978102	20011017 <--
	US 6828316	B2	20041207		
PRAI	JP 1996-222770	A	19960823		
	WO 1997-JP2882	W	19970820		
	US 1999-147711	A3	19990223		

OS MARPAT 128:192678
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
TI Preparation of N,N'-bis(aralkenyl)piperazine and -homopiperazines as inhibitors of cellular adhesion and infiltration.
GI



I

AB Title compds. (I; X = (CH2)n; R1-R6 = H, halo, OH, alkyl, alkoxy; m = 1-3; n = 2, 3), were prepared Thus, (E)-5-(3,4,5-trimethoxyphenyl)-4-pentenyl bromide, homopiperazine, K2CO3, KI, and DMF were heated at 100° to give N,N'-bis[(E)-(3,4,5-trimethoxyphenyl)-4-pentenyl]homopiperazine (II). II at 30 mg/kg i.p. in guinea pigs reduced infiltration of trachea by eosinocytes from 204.5 cells/mm to 122.2 cells/mm. II tablet and capsule formulations are given.
AN 1997:435944 CAPLUS
DN 127:50669
TI Preparation of N,N'-bis(aralkenyl)piperazine and -homopiperazines as inhibitors of cellular adhesion and infiltration.
IN Nakao, Hiroshi; Umetani, Michihisa; Suda, Makoto; Nagoya, Takao
PA Kowa Co., Ltd., Japan
SO Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 774257	A2	19970521	EP 1996-118463	19961118 <--
	EP 774257	A3	19970827		
	R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 09143075	A2	19970603	JP 1995-301526	19951120 <--
	US 5723465	A	19980303	US 1996-746811	19961118 <--
PRAI	JP 1995-301526	A	19951120		

OS MARPAT 127:50669

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FULL ESTIMATED COST	40.85	63.02

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION

Eryhtropoietin production potentiator

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LOGOFF? (Y)/N/HOLD:y

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FULL ESTIMATED COST	0.06	63.08

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-6.00

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